

REMARKS

In the Claims:

Applicants thank the Examiner for withdrawing the 35 U.S.C. § 112, second paragraph rejections of Claims 25-27, 31, 35, and 38-41 raised in the Office Action of September 24, 2003.

In the Response and Request for Reconsideration submitted December 24, 2003, although Applicants argued against the Examiners rejections of claim 35, Applicants erroneously indicated, in the listing of the claims, that claim 35 was canceled. In the office action mailed April 19, 2004, the Examiner recognized that claim 35 is pending in the application. Applicants have corrected the listing of the claims in this response such that claim 35 is no longer indicated as being canceled. In addition, Applicants have amended claim 35 to clarify that the claimed isolated nucleic acid hybridizes under high stringency conditions selected from the group consisting of: (i) 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (ii) 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6/5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; and (iii) 50% formamide, 5 x SSC (0.75 M sodium chloride, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% sodium dodecyl sulphate, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (0.75 M sodium chloride, 0.075 M sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC (0.75 M sodium chloride, 0.075 N sodium citrate) containing EDTA at 55°C.

Claims 42 and 43 are canceled herein without prejudice or disclaimer.

Priority Determination:

The Examiner has found that the present application has an effective priority date of 12/22/98, based on the filing date of U.S. Provisional Application Serial Number 60/113,296.

Claim Rejections:

35 U.S.C. § 102(e)

The Examiner has rejected claims 25-27, 31, 35, 38-41 and 43 under 35 U.S.C. § 102(e) as being anticipated by Holtzman *et al.*, U.S. Patent Application Publication US20020028508, effective filing date, April 23, 1998. Previously, Applicants relied on *Elan Pharm., Inc. v. Mayo Found. for Med. Ed. & Research* and *Verdegaal Bros. v. Union Oil Co. of California*, and argued that Holtzman *et al.* is not an anticipatory reference because it does not enable the present invention. Additionally, Applicants previously argued that Holtzman *et al.* does not anticipate the present invention because it fails to anticipate each and every element of the presently claimed invention.

In the office action mailed April 19, 2004, the Examiner rejected Applicants' arguments as well as Applicants reliance on *Elan Pharm., Inc. v. Mayo Found. for Med. Ed. & Research* and *Verdegaal Bros. v. Union Oil Co. of California*. Applicants respectfully disagree with the Examiner's analysis and maintain that Holtzman *et al.* is not a proper anticipatory reference because it does not enable the claimed invention that it is alleged to anticipate and because it does not disclose every element of the claimed invention.

In any event, Applicants additionally submit that Holtzman *et al.* does not anticipate the present invention because Applicants sequenced and isolated the claimed nucleic acid prior to the time Holtzman *et al.* was filed. Anticipation under 35 U.S.C. § 102(e) requires that the invention being claimed be "described in (1) an application for a patent, published under section 122(b), by another filed in the United States *before the invention by the applicant for patent.*" (emphasis added). More specifically, Applicants sequenced and isolated the claimed nucleic acid before the April 23, 1998 filing date of Holtzman, as is evidenced by the disclosure of the nucleic acid claimed in the present

application in U.S. Provisional Application Serial Number 60/069,702, filed 12/16/97.

Therefore, Holtzman is not an anticipatory reference under 35 U.S.C. § 102(e).

In support of this argument, Applicants respectfully direct the Examiner's attention to the attached declarations of David Botstein, Audrey Goddard, Paul Godowski, Christopher Grimaldi, Austin Gurney, Margaret Roy, and William Wood under 37 C.F.R. § 1.131. Each of these declarations demonstrates that the nucleic acid and amino acid sequences of the present invention were completed prior to the effective date of the alleged anticipatory reference.

As support for the argument that these declarations overcome the Holtzman reference, the Examiner is first respectfully directed to *In re Stempel*, 113 USPQ 77 (CCPA 1957), where, similar to the present situation, the patent applicant, Stempel, had claims directed to both (i) a particular genus of chemical compounds (the "genus" claim) and (ii) a single species of chemical compound that was encompassed within that genus (the "species" claim). In support of a rejection under 35 U.S.C. § 102, the examiner cited a prior art reference that disclosed the exact chemical compound recited in Stempel's "species" claim. In response to the rejection, Stempel filed a declaration under 37 C.F.R. § 1.131 demonstrating that he possessed that specific chemical compound prior to the effective date of the cited prior art reference. The lower court found the 131 declaration effective to "swear back" of the prior art reference for purposes of allowing a claim to the specific species. However, the lower court relied on the doctrine that prior disclosure of a species is sufficient to anticipate a later claim to a genus encompassing that species to rule the 131 declaration ineffective for swearing behind the cited references for purposes of the "genus" claim.

On appeal, however, the CCPA reversed the decision of the lower court and found Stempel's 131 declaration effective for swearing behind the cited reference for purposes of *both* the "species" claim and the "genus" claim. Specifically, the CCPA stated:

"We are convinced that under the law all the applicant can be required to show [in a declaration under 37 C.F.R. § 1.131] is priority with respect to so much of the claimed invention as the reference happens to show. When he has done this he has disposed of the reference." (*Id.* at 81; emphasis supplied).

Thus, the "Stempel Doctrine" stands for the clear proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he/she made *that portion of the claimed invention* that is disclosed in the prior art reference before the date of the reference. In other words, a patent applicant need not demonstrate that he/she made the entire claimed invention in order to remove a cited prior art reference under 37 C.F.R. § 1.131...to the contrary, he/she only need show prior possession of that portion of the claimed invention that is disclosed in the prior art reference.

The Examiner is also directed respectfully to *In re Clarke*, 148 USPQ 665 (CCPA 1966), which further clarifies the applicability of the Stempel Doctrine to the present situation. Clarke, the patent applicant in *In re Clarke*, filed a patent application claiming a genus of chemical compounds. The reference cited against the Clarke application was a publication showing one species falling within the scope of Clarke's generic claim. In response, Clarke submitted a declaration under 37 C.F.R. § 1.131 demonstrating that he had conceived of the claimed genus of chemical compounds and actually reduced to practice one species of the genus. However, that species was different from the one disclosed in the cited reference. In other words, Clarke was not able to show that he had actually reduced to practice the same chemical compound that was disclosed in the cited prior art reference. Thus, unlike the patent application in the *In re Stempel* case described above, Clarke did not show complete prior possession of the species disclosed in the cited prior art reference. Nevertheless, the CCPA held Clarke's 131 declaration effective if he showed that reduction to practice of the one species was sufficient to substantiate a claim to the whole genus which included the species disclosed in the reference. The CCPA indicated that such substantiation is provided if the reference species would have been obvious to one of ordinary skill in the art, in light

of what the applicant had completed prior to the disclosure of the reference species. Specifically, the CCPA stated:

"the [Stempel] rule for antedating references is not limited to fact situations where the inventor can show priority to the *identical* compound described in the reference...[a]n applicant should not be prevented from obtaining a patent to an invention where a compound described in a reference would have been obvious to one of ordinary skill in the art in view of what the applicant proves was completed with respect to the invention prior to the effective date of the reference...[W]here it can be concluded that facts, offered in a rule 131 affidavit in support of a general allegation of conception and reduction to practice of the invention, would persuade one of ordinary skill in the art to a reasonable certainty that the applicant possessed so much of the invention as to encompass the reference disclosure, then that showing should be accepted as establishing *prima facie* a case of inventorship prior to the reference...Upon satisfying that test, species of the reference falling within the claim may be antedated indirectly." (*Id.* at 669-70, emphasis supplied).

Thus, *In re Clarke* clarifies that the Stempel Doctrine described above extends to situations such as the present situation, where the specific sequence disclosed in the allegedly anticipatory reference is not identical to the sequence actually reduced to practice by Applicants.

More specifically, the attached declarations of Botstein *et al.* demonstrate that Applicants isolated and sequenced DNA44176, (SEQ ID NO:49 in the present application) before the filing date of Holtzman *et al.* Holtzman *et al.* disclose a nucleic acid sequence that is 94.1% similar to SEQ ID NO:49, with 98% similarity at localized segments. Holtzman *et al.* also disclose an amino acid sequence that is 96.8% identical to SEQ ID NO:50 of the present application. The presently claimed genus encompasses sequences that are at least 95% identical to SEQ ID NO:49 or to the nucleic acid encoding SEQ ID NO:50. Thus, the amino acid sequence of Holtzman and at least the localized similarity segments of the nucleic acid sequence of Holtzman fall within the same genus as Applicants sequence disclosed in U.S. Provisional Application No. 60,069,702, filed 12/16/1997.

As stated in *In re Clarke*, the Stempel Doctrine applies if (1) the compound disclosed in Holtzman *et al.* and the compound reduced to practice by Applicants fall within the same genus and (2) the Holtzman species would have been obvious to one of ordinary skill in the art in light of what Applicants had completed prior to the disclosure of the Holtzman species, *i.e.* Applicants had conceived of the genus prior to Holtzman's disclosure of a species falling within the genus.

As discussed above, the first condition from *In re Clarke* is satisfied in this case. In addition, the declarations of David Botstein *et al.*, demonstrate that Applicants had reduced DNA44176 to practice and had conceived a genus of variant sequences based on DNA44176. In particular, as the inventors attest, they appreciated that the invention of DNA44176 included variant sequences at the time they reduced the invention to practice. Numerous passages in U.S. Provisional Application Serial No. 60/069,702 indicate that the inventors conceived of a genus of nucleic acids encoding PRO347. In particular, the passages of the specification quoted in paragraphs 6-10 of the declarations of Wood, Goddard, and Gurney demonstrate this. Specifically, in paragraph 6, the inventors declare that the definition of "native sequence PRO347 polypeptide" found at page 4 of the '702 application includes:

naturally-occurring truncated or secreted forms of a PRO347 polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of a PRO347 polypeptide.

In addition, at paragraph 7, the inventors declare that at page 7 of the '702 application they explained that the invention included variants:

In addition to the full-length native sequence PRO347 polypeptide described herein, it is contemplated that PRO347 variants can be prepared. PRO347 variants can be prepared by introducing appropriate nucleotide changes into the PRO347-encoding DNA, or by synthesis of the desired PRO347 polypeptide.

Further, each inventor declares in paragraph 8:

As one of skill in the art, I appreciated at the time DNA44176 was sequenced, that variations could be made using methods known in the art such as

oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Techniques for achieving sequence variation using site-directed mutagenesis are described in Carter *et al.*, *Nucleic Acids Res.*, 13:4431 (1985) (attached hereto as Exhibit A) and Zoller *et al.*, *Nucleic Acids Res.*, 10:6487 (1982) (attached hereto as Exhibit B). Techniques for achieving sequence variation using cassette mutagenesis are described in Wells *et al.*, *Gene* 34:315 (1985) (attached hereto as Exhibit C). These techniques were described in the '702 application at page 8.

Additionally, the described uses of PRO347, found at page 17 of the '702 application indicate that the invention includes variant sequences, as the inventors declare at paragraph 9:

Nucleotide sequences (or their complement) encoding PRO347 polypeptides have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA. PRO347-encoding nucleic acid will also be useful for the preparation of PRO347 polypeptides by the recombinant techniques described herein. ... The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related PRO347 sequences.

Each inventor also declares, in paragraph 10, that one of these uses was described in Example 2, found at page 27 of the '702 application:

DNA comprising the coding sequence of full-length PRO347 (as shown in Figure 1, SEQ ID NO:1) is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO347) in human tissue cDNA libraries or human tissue genomic libraries.

The declarations of Botstein *et al.*, clearly demonstrate that Applicants had conceived a genus of PRO347 sequences by the time the '702 application was filed. Therefore, these declarations fully meet the requirements of both *In re Stempel* and *In re Clarke* and Holtzman *et al.*, has been removed as an anticipatory reference. Applicants respectfully request the rejection be withdrawn.

Additionally, Applicants note that in determining priority for the present application, the Examiner determined that Applicants were not entitled to claim priority to U.S. Provisional Application No. 60/069,702 because the Examiner alleges that application does not provide any utility for the disclosed sequence. Applicants respectfully

disagreed with the Examiner's determination. In any event, under the Stempel Doctrine, Applicants may rely on the disclosure of the sequence of SEQ ID NO:49 in U.S. Provisional Application NO. 60/069,702 to antedate the Holtzman reference even if the Examiner maintains that U.S. Provisional Application No. 60/069.702 does not provide a utility for the disclosed sequence.

In particular, the Examiner is respectfully directed to *In re Moore*, 170 USPQ 260 (CCPA 1971), where the Stempel doctrine was extended to cases where, as in the present case, a reference disclosed a claimed compound but failed to disclose a sufficient utility for it. More specifically, the patent applicant, Moore, claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the examiner cited a reference disclosing the claimed PFDC compound, but not a utility for such compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131, demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had yet to establish a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to effective date of the cited prior art reference, he had not yet completed his "invention."

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relying on the Stempel Doctrine, stated:

"The determination of a practical utility when one is not obvious need not have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes." (*Id.* at 267, emphasis supplied).

Thus, *In re Moore* confirms the Stempel Doctrine holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of the claimed invention that appears in the cited reference.

Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either with or absent a utility different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant only needs to demonstrate that he or she had possession of the claimed chemical compound before the effective date of the prior art reference.

As argued in the Amendment and Request for Reconsideration submitted 24 December 2003, Holtzman *et al.* does not disclose either a specific and substantial utility or a well-established utility for the sequence disclosed therein. Thus, Applicants are not required to show a utility to antedate Holtzman, but rather are only required to show prior conception of the genus and sequence presently claimed. Hence, considered in light of the Stempel Doctrine, as extended by *In re Clarke* and *In re Moore*, the declarations of inventors Botstein *et al.* demonstrate that Holtzman *et al.* does not anticipate the presently claimed invention and Applicants respectfully request that this ground of rejection be withdrawn.

35 U.S.C. § 112, second paragraph

Claims 42 and 43 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner contends that the conservative amino acid substitutions do not set a limitation on the number of possible substitutions. Additionally, the Examiner states that the wording of claim 43 is unclear as to the number or length of the claimed additions and deletions. The Examiner kindly notes that this rejection can be overcome by alteration of the claim language. Applicants respectfully cancel Claims 42 and 43 herein without prejudice or disclaimer. Thus, Applicants have overcome rejection of claims 42 and 43 and respectfully request this rejection be withdrawn.

35 U.S.C. § 112, first paragraph

Written Description

Claims 25-26, 35, and 38-41 remain rejected and new claims 42 and 43 are rejected under 35 U.S.C. § 112, first paragraph for failure to satisfy the written description requirement. Specifically, the Examiner alleges that Claims 25-26, 35, and 38-43 contain subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time of the application, had possession of the claimed invention.

Applicants have herein canceled claims 42 and 43 without prejudice or disclaimer. Applicants previously argued that they had demonstrated possession of the claimed invention by disclosing SEQ ID NOS: 49 and 50, as well as by depositing DNA44176 (ATCC deposit no. ATCC209532). Additionally, Applicants argued that under the analysis of Example 14 of the Revised Interim Written Description Guidelines Training Materials ("Written Description Training Materials"), Applicants satisfied the written description requirement for claims 25-26, 35, and 38-41.

In the office action mailed April 19, 2004, the Examiner rejects these arguments and argues that the present claims are more analogous to those found in Example 11 of the Written Description Training Materials. Based on a comparison between the present claims and those set forth in Example 11, the Examiner alleges that the written description requirement is not satisfied in the present application.

Applicants respectfully disagree with the Examiner's analysis of Example 11 of the Written Description Training Materials and submit that Claims 25-26, 35, and 38-41 are adequately described in the present application.

Applicants respectfully disagree with the Examiner's analysis of Claim 1 of Example 11 from the Written Description Training Materials. Claim 1 of example 11 is directed to a genus of DNA sequences that encode protein X. Although only a single species within

that genus is disclosed, Example 11 explains that the genus is adequately described because a genetic code table could be used to create the claimed genus.

The Examiner argues that the written description requirement is satisfied for Claim 1 of Example 11 because the protein encoded by the claimed DNA was known, as well as its function, and therefore, had a specific and substantial utility. The Examiner argues that the present situation differs from Claim 1 of Example 11 because according to the Examiner, the function of the protein encoded by SEQ ID NO:49 of the present invention is not known and the utility is based on amplification of the DNA in tumors, such that any polynucleotide encoding the protein might not meet the written description requirement.

Applicants respectfully disagree. In particular, the claims of the present application are directed to nucleic acids that have the characteristic of being amplified in lung or colon tumors. As such, the claims are supported by a diagnostic utility. Hence, although a function of the protein encoded by the claimed nucleic acid is unknown, a utility of the claimed nucleic acid is described in the specification. In any event, as discussed below, the application sets forth distinguishing identifying characteristics that are sufficiently detailed to show that the applicant was in possession of the claimed invention and therefore, Applicants have satisfied the written description requirement.

Applicants also respectfully disagree with the Examiner that Claim 27 is similar to Claim 2 in Example 11. The analysis rejecting Claim 2 in Example 11 focuses on the application of a single allele to identify similar but unknown alleles by using a hybridization procedure. Claim 27 is directed to the wild type DNA sequence disclosed in the specification and therefore, Applicants respectfully submit that Claim 2 in Example 11 is not applicable to claim 27. In addition, Applicants note that the Examiner has not rejected claim 27 for lack of written description. Further, according to the training materials Claim 2 of Example 11 is not adequately described because there is no description of how one allele is representative of another allele in the genus. That is, there is no description of the common attributes of the genus. The description set forth in the present application differs significantly from the description of Example 11

because as discussed below, the present application sets forth distinguishing identifying characteristics that are sufficiently detailed to show that the applicant was in possession of the claimed invention.

The Examiner also rejects claim 25 based on claim 3 of Example 11, stating that since only one sequence has been disclosed; there is no evidence in the specification that other embodiments exist. Applicants respectfully disagree.

The written description requirement does not require an inventor to actually physically possess his invention. MPEP § 2163. Possession of an invention may be shown in a variety of ways. If an application does not describe an actual reduction to practice, reduction to drawings or structural or chemical formula, as is the case here, the application may still set forth an adequate written description of the invention if the application sets forth distinguishing identifying characteristics that are sufficiently detailed to show that the applicant was in possession of the claimed invention. *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). According to MPEP § 2163 (i)(C)(2):

Whether a specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

Applicants have satisfied the written description requirement because they have disclosed a combination of identifying characteristics sufficient to distinguish the claimed invention from other materials. Specifically, Applicants have disclosed structure,

physical and/or chemical properties, functional characteristics and a method of making the claimed invention.

First, Applicants have disclosed structure by disclosing the nucleic acid sequence of PRO347, SEQ ID NO: 49. Further, those of skill in the art, reading the specification would appreciate that the invention of SEQ ID NO:49 was not limited to only this sequence, but that the inventors contemplated and described a genus of sequences with at least 95% sequence identity to SEQ ID NO: 49. For example, at pages 60-61 of the specification, Applicants disclose methods of making substitutions, as well as substitutions themselves, which could be used to obtain a nucleic acid sequence variant of the claimed invention, that is one that shares at least 95% sequence identity with SEQ ID NO:49 and that maintains the characteristic of being amplified in lung or colon tumors. Currently rejected claims 25-26 are directed to such nucleic acids. Currently rejected claim 35 is directed to nucleic acids that hybridize to SEQ ID NO: 49 (or to the nucleic acid encoding SEQ ID NO: 50) under high stringency conditions, and that maintain the characteristic of being amplified in lung or colon tumors.

In addition to describing the structure of the sequence of SEQ ID NO:49, at page 103, lines 21-29 of the specification, Applicants have disclosed physical and chemical features of SEQ ID NO: 49, which would likely be common to nucleic acids that share at least 95% sequence identity with SEQ ID NO: 49. In addition, Figure 20 discloses further features of the encoded polypeptide, which would likely be common to all polypeptides encoded by the claimed genus. Even further, at page 59, Applicants describe variant sequences and explain that:

Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology....The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing

the resulting variants for activity exhibited by the full-length or mature native sequence.

One of ordinary skill in the art would appreciate that the above disclosure also applies to nucleic acids and would appreciate the relationship between amino acids and nucleic acids.

Claims 25-26 and 35 also require that the claimed nucleic acid variants have the characteristic of being amplified in lung or colon tumors. The Examiner disagrees that being "amplified in lung or colon tumors" is a "function" of the claimed nucleic acid. In any event, as discussed above, a claim to a genus may be adequately described by description of *characteristics* that are common to the genus and allow those of skill in the art to determine whether a particular species falls within the scope of the genus. MPEP § 2163. Being "amplified in lung or colon tumors" is one characteristic which distinguishes members of the claimed genus from other nucleic acids.

In addition to describing structure, physical and chemical properties and characteristics of the claimed nucleic acids, Applicants also have disclosed how to "make" the claimed invention. Specifically, as discussed previously, at pages 122-137, Applicants disclose an assay for identifying and isolating the nucleic acids of the claimed invention. More specifically, at pages 122-124 of the specification, Applicants teach that SEQ ID NO: 49 may be isolated from lung or colon tumors. One of skill in the art would appreciate that nucleic acids that are at least 95% identical to SEQ ID NO:49 may also be isolated from lung or colon tumors. At pages 23-29, and at Table 1, pages 34-54, the specification teaches one of ordinary skill in the art how to determine whether a particular sequence is 95-99% identical to a sequence such as SEQ ID NO: 49. Pages 124-137 of the specification teach one of skill in the art a method for assaying for gene amplification in lung or colon tumors.

Thus, based on the above combination of described factors, Applicants have provided an adequate written description of the invention encompassed by the claims and respectfully request that the Examiner withdraw this ground of rejection.

Finally, the Examiner argues that the claims require the nucleic acid to be amplified in lung or colon tumors and therefore, according to the Examiner, the claims are limited to naturally occurring, not engineered nucleic acids. Applicants respectfully disagree. The claims do not require that the claimed nucleic acid be *isolated* from lung or colon tumors. Rather, the claims require the claimed nucleic acid to have the characteristic of being amplified in lung or colon tumors.

One of ordinary skill in the art would appreciate, after reading the present application, that it is possible to engineer a nucleic acid that is at least 95% identical to SEQ ID NO:49 and that has the characteristic of being amplified in lung or colon tumors. More specifically, pages 59-62 of the specification discuss engineering variant sequences using the PRO sequences disclosed in the specification. For example, to create a variant sequence of PRO347, the specification teaches that one of ordinary skill in the art may use a variety of techniques, including oligonucleotide-mediated mutagenesis, alanine scanning, PCR mutagenesis, site-directed mutagenesis, cassette mutagenesis, or restriction selection mutagenesis to achieve variation in a PRO sequence. Page 59 of specification also provides guidance as to where additions, deletions or substitutions should be made in a sequence to achieve a sequence that maintains the function or characteristics of the wild type PRO sequence.

For all of these reasons, Applicants have overcome the rejection of claims 25-26, 35, and 38-41 for lack of written description and respectfully request that this rejection be withdrawn.

SUMMARY

Applicants believe that currently pending Claims 25-35 and 38-41 are patentable. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite allowance of this application.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of)
Botstein et al.)
Serial No. 09/944,896) Examiner: Eileen B. O'Hara
Filed: August 31, 2001) Group Art Unit: 1646
Title: SECRETED AND)
TRANSMEMBRANE)
POLYPEPTIDES AND NUCLEIC)
ACIDS ENCODING THE SAME)

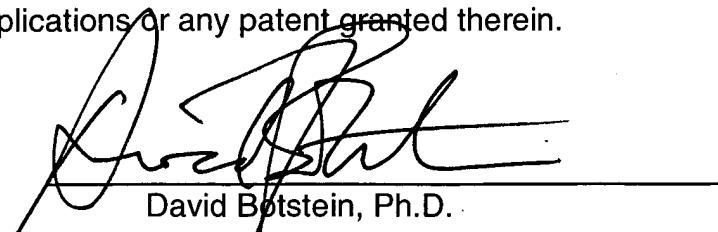
The Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

DECLARATION PURSUANT TO 37 CFR 1.131

I, David Botstein, Margaret Roy, and J. Christopher Grimaldi declare as follows:

1. I am one of the seven named inventors of the claimed subject matter of U.S. Patent Application Serial No. 09/944,896 ("the '896 application").
2. I was employed by Genentech, Inc., South San Francisco, CA 94080 when I invented the invention encompassed by the claims of the '896 application.
3. I understand the Examiner of the '896 application has cited Holtzman *et al.*, U.S. Patent Publication No. 20020028505 against the '896 application, alleging that the Holtzman sequence anticipates, under 35 U.S.C. § 102(e), the invention claimed in the '896 application.
4. I did not play a role in the sequencing or cloning of DNA44176 but did gene amplification or tissue expression work using DNA44176.
5. To the best of my knowledge, I agree that the statements of my co-inventors, relating to the sequencing and cloning of DNA44176, are true and correct.
6. I declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that

these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above applications or any patent granted therein.



David Botstein, Ph.D.

7-23-04

Date

Margaret Roy, Ph.D.

Date

J. Christopher Grimaldi, Ph.D.

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of)
Botstein et al.)
Serial No. 09/944,896) Examiner: Eileen B. O'Hara
Filed: August 30, 2001) Group Art Unit: 1646
Title: SECRETED AND)
TRANSMEMBRANE)
POLYPEPTIDES AND NUCLEIC)
ACIDS ENCODING THE SAME)

The Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

DECLARATION PURSUANT TO 37 CFR 1.131

I, Audrey Goddard, declare as follows:

1. I am Senior Clinical Scientist at the Diagnostics, Development Sciences Department of Genentech, Inc., South San Francisco, CA 94080.
2. I am one of the seven named inventors of the claimed subject matter of U.S. Patent Application Serial No. 09/944,896 ("the '896 application").
3. Prior to April 23, 1998, the effective filing date of U.S. Patent Application Publication No. US20020028508 (U.S. Application Serial No. 09/065,661), I conceived and reduced to practice in the United States the nucleic acid sequence identified as DNA44176, which encodes PRO347 (and is referred to as SEQ ID NO:49 in the '896 application). I disclosed DNA44176 in U.S. Provisional Application Serial No. 60/069,702 ("the '702 application"), filed 12/10/97.

4. The attached sequence listing is a true and correct copy of the nucleic acid sequence of DNA44176, as set forth in the '702 application.
5. Upon isolating and sequencing DNA44176, I appreciated that the invention of DNA44176 included variant sequences, such as allelic variant sequences, variant sequences that arise due to the degeneracy of the genetic code, and variant sequences that arise naturally or synthetically due to additions, deletions or substitutions of nucleic acids.
6. For example, in the '702 application we defined "native sequence PRO347 polypeptide" at page 4 as specifically encompassing:

naturally-occurring truncated or secreted forms of a PRO347 polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of a PRO347 polypeptide.

7. Also, in the '702 application, we noted, at page 7:

In addition to the full-length native sequence PRO347 polypeptide described herein, it is contemplated that PRO347 variants can be prepared. PRO347 variants can be prepared by introducing appropriate nucleotide changes into the PRO347-encoding DNA, or by synthesis of the desired PRO347 polypeptide.
8. As one of skill in the art, I appreciated at the time DNA44176 was sequenced, that variations could be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Techniques for achieving sequence variation using site-directed mutagenesis are described in Carter *et al.*, *Nucleic Acids Res.*, 13:4431 (1985) (attached hereto as Exhibit A) and Zoller *et al.*, *Nucleic Acids Res.*, 10:6487 (1982) (attached hereto as Exhibit B). Techniques for achieving sequence variation using cassette mutagenesis are described in Wells *et al.*, *Gene* 34:315 (1985) (attached hereto as Exhibit C). These techniques were described in the '702 application at page 8.

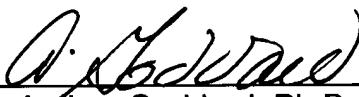
9. Further, as one of skill in the art, I appreciated that there were numerous uses for PRO347 and its variant sequences. Some of these uses are disclosed at page 17 of the specification:

Nucleotide sequences (or their complement) encoding PRO347 polypeptides have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA. PRO347-encoding nucleic acid will also be useful for the preparation of PRO347 polypeptides by the recombinant techniques described herein. ... The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related PRO347 sequences.

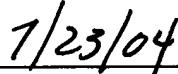
10. We described one of these uses in Example 2, found at page 27 of the '702 application. Specifically, we explained the use of PRO-347-encoding DNA as a hybridization probe:

DNA comprising the coding sequence of full-length PRO347 (as shown in Figure 1, SEQ ID NO:1) is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO347) in human tissue cDNA libraries or human tissue genomic libraries.

11. I declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above applications or any patent granted therein.



Audrey Goddard, Ph.D.



Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of)
Botstein et al.)
Serial No. 09/944,896) Examiner: Eileen B. O'Hara
Filed: August 30, 2001) Group Art Unit: 1646
Title: SECRETED AND)
TRANSMEMBRANE)
POLYPEPTIDES AND NUCLEIC)
ACIDS ENCODING THE SAME)

The Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

DECLARATION PURSUANT TO 37 CFR 1.131

I, Paul Godowski, declare as follows:

1. I am a Staff Scientist in the Department of Immunology of Genentech, Inc., South San Francisco, CA 94080..
2. I am one of the seven named inventors of the claimed subject matter of U.S. Patent Application Serial No. 09/944,896 ("the '896 application").
3. Prior to April 23, 1998, the effective filing date of U.S. Patent Application Publication No. US20020028508 (U.S. Application Serial No. 09/065,661), I conceived and reduced to practice in the United States the nucleic acid sequence identified as DNA44176, which encodes PRO347 (and is referred to as SEQ ID NO:49 in the '896 application). I disclosed DNA44176 in U.S. Provisional Application Serial No. 60/069,702 ("the '702 application"), filed 12/10/97.

4. The attached sequence listing is a true and correct copy of the nucleic acid sequence of DNA44176, as set forth in the '702 application.
5. Upon isolating and sequencing DNA44176, I appreciated that the invention of DNA44176 included variant sequences, such as allelic variant sequences, variant sequences that arise due to the degeneracy of the genetic code, and variant sequences that arise naturally or synthetically due to additions, deletions or substitutions of nucleic acids.
6. For example, in the '702 application we defined "native sequence PRO347 polypeptide" at page 4 as specifically encompassing:

naturally-occurring truncated or secreted forms of a PRO347 polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of a PRO347 polypeptide.

7. Also, in the '702 application, we noted, at page 7:
8. In addition to the full-length native sequence PRO347 polypeptide described herein, it is contemplated that PRO347 variants can be prepared. PRO347 variants can be prepared by introducing appropriate nucleotide changes into the PRO347-encoding DNA, or by synthesis of the desired PRO347 polypeptide.
8. As one of skill in the art, I appreciated at the time DNA44176 was sequenced, that variations could be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Techniques for achieving sequence variation using site-directed mutagenesis are described in Carter *et al.*, *Nucleic Acids Res.*, 13:4431 (1985) (attached hereto as Exhibit A) and Zoller *et al.*, *Nucleic Acids Res.*, 10:6487 (1982) (attached hereto as Exhibit B). Techniques for achieving sequence variation using cassette mutagenesis are described in Wells *et al.*, *Gene* 34:315 (1985) (attached hereto as Exhibit C). These techniques were described in the '702 application at page 8.

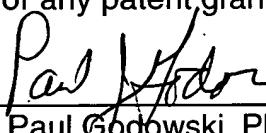
9. Further, as one of skill in the art, I appreciated that there were numerous uses for PRO347 and its variant sequences. Some of these uses are disclosed at page 17 of the specification:

Nucleotide sequences (or their complement) encoding PRO347 polypeptides have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA. PRO347-encoding nucleic acid will also be useful for the preparation of PRO347 polypeptides by the recombinant techniques described herein. ... The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related PRO347 sequences.

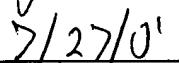
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DNA comprising the coding sequence of full-length PRO347 (as shown in Figure 1, SEQ ID NO:1) is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO347) in human tissue cDNA libraries or human tissue genomic libraries.

11. I declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above applications or any patent granted therein.



Paul Godowski, Ph.D.



Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of)
Botstein et al.)
Serial No. 09/944,896) Examiner: Eileen B. O'Hara
Filed: August 30, 2001) Group Art Unit: 1646
Title: SECRETED AND)
TRANSMEMBRANE)
POLYPEPTIDES AND NUCLEIC)
ACIDS ENCODING THE SAME)

The Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

DECLARATION PURSUANT TO 37 CFR 1.131

I, David Botstein, Margaret Roy, and J. Christopher Grimaldi declare as follows:

1. I am one of the seven named inventors of the claimed subject matter of U.S. Patent Application Serial No. 09/944,896 ("the '896 application").
2. I was employed by Genentech, Inc., South San Francisco, CA 94080 when I invented the invention encompassed by the claims of the '896 application.
3. I understand the Examiner of the '896 application has cited Holtzman et al., U.S. Patent Publication No. 20020028505 against the '896 application, alleging that the Holtzman sequence anticipates, under 35 U.S.C. § 102(e), the invention claimed in the '896 application.
4. I did not play a role in the sequencing or cloning of DNA44176 but did gene amplification or tissue expression work using DNA44176.
5. To the best of my knowledge, I agree that the statements of my co-inventors, relating to the sequencing and cloning of DNA44176, are true and correct.
6. I declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that

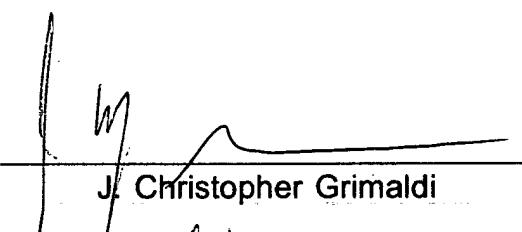
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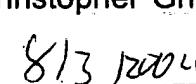
David Botstein, Ph.D.

Date

Margaret Roy, Ph.D.

Date


J. Christopher Grimaldi


8/13/2004

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of)
Botstein et al.)
Serial No. 09/944,896) Examiner: Eileen B. O'Hara
Filed: August 31, 2001) Group Art Unit: 1646
Title: SECRETED AND)
TRANSMEMBRANE)
POLYPEPTIDES AND NUCLEIC)
ACIDS ENCODING THE SAME)

The Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

DECLARATION PURSUANT TO 37 CFR 1.131

I, Austin Gurney, declare as follows:

1. I am Senior Scientist at the Molecular Biology Department of Genentech, Inc., South San Francisco, CA 94080.
2. I am one of the seven named inventors of the claimed subject matter of U.S. Patent Application Serial No. 09/944,896 ("the '896 application").
3. Prior to April 23, 1998, the effective filing date of U.S. Patent Application Publication No. US20020028508 (U.S. Application Serial No. 09/065,661), I conceived and reduced to practice in the United States the nucleic acid sequence identified as DNA44176, which encodes PRO347 (and is referred to as SEQ ID NO:49 in the '896 application). I disclosed DNA44176 in U.S. Provisional Application Serial No. 60/069,702 ("the '702 application"), filed 12/10/97.

4. The attached sequence listing is a true and correct copy of the nucleic acid sequence of DNA44176, as set forth in the '702 application.
5. Upon isolating and sequencing DNA44176, I appreciated that the invention of DNA44176 included variant sequences, such as allelic variant sequences, variant sequences that arise due to the degeneracy of the genetic code, and variant sequences that arise naturally or synthetically due to additions, deletions or substitutions of nucleic acids.
6. For example, in the '702 application we defined "native sequence PRO347 polypeptide" at page 4 as specifically encompassing:

naturally-occurring truncated or secreted forms of a PRO347 polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of a PRO347 polypeptide.

7. Also, in the '702 application, we noted, at page 7:

In addition to the full-length native sequence PRO347 polypeptide described herein, it is contemplated that PRO347 variants can be prepared. PRO347 variants can be prepared by introducing appropriate nucleotide changes into the PRO347-encoding DNA, or by synthesis of the desired PRO347 polypeptide.
8. As one of skill in the art, I appreciated at the time DNA44176 was sequenced, that variations could be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Techniques for achieving sequence variation using site-directed mutagenesis are described in Carter *et al.*, *Nucleic Acids Res.*, 13:4431 (1985) (attached hereto as Exhibit A) and Zoller *et al.*, *Nucleic Acids Res.*, 10:6487 (1982) (attached hereto as Exhibit B). Techniques for achieving sequence variation using cassette mutagenesis are described in Wells *et al.*, *Gene* 34:315 (1985) (attached hereto as Exhibit C). These techniques were described in the '702 application at page 8.

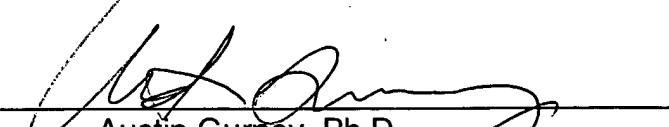
9. Further, as one of skill in the art, I appreciated that there were numerous uses for PRO347 and its variant sequences. Some of these uses are disclosed at page 17 of the specification:

Nucleotide sequences (or their complement) encoding PRO347 polypeptides have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA. PRO347-encoding nucleic acid will also be useful for the preparation of PRO347 polypeptides by the recombinant techniques described herein. ... The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related PRO347 sequences.

10. We described one of these uses in Example 2, found at page 27 of the '702 application. Specifically, we explained the use of PRO-347-encoding DNA as a hybridization probe:

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11. I declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above applications or any patent granted therein.



Austin Gurney, Ph.D.

7/27/04

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of)
Botstein et al.)
Serial No. 09/944,896) Examiner: Eileen B. O'Hara
Filed: August 30, 2001) Group Art Unit: 1646
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TRANSMEMBRANE)
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ACIDS ENCODING THE SAME)

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P.O. Box 1450
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DECLARATION PURSUANT TO 37 CFR 1.131

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David Botstein, Ph.D.

Date



Margaret Roy, Ph.D.



Date

J. Christopher Grimaldi, Ph.D.

Date

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The Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

DECLARATION PURSUANT TO 37 CFR 1.131

I, William Wood, declare as follows:

1. I am Director and Staff Scientist at the Diagnostics, Development Sciences Department of Genentech, Inc., South San Francisco, CA 94080.
2. I am one of the seven named inventors of the claimed subject matter of U.S. Patent Application Serial No. 09/944,896 ("the '896 application").
3. Prior to April 23, 1998, the effective filing date of U.S. Patent Application Publication No. US20020028508 (U.S. Application Serial No. 09/065,661), I conceived and reduced to practice in the United States the nucleic acid sequence identified as DNA44176, which encodes PRO347 (and is referred to as SEQ ID NO:49 in the '896 application). I disclosed DNA44176 in U.S. Provisional Application Serial No. 60/069,702 ("the '702 application"), filed 12/10/97.

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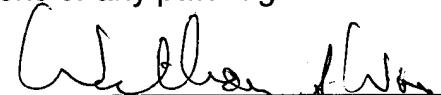
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William Wood, Ph.D.



Date